UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,018	03/16/2001	James Robl	P 0279159	6620

909 7590 07/01/2003

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,018	ROBL ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed 4/10/03, Paper No. 6, has been entered. Claims 1-35 have been cancelled. Claims 36-52 have been added.

Any rejection made of record in the prior Office action, mailed 8/15/02, Paper No. 5, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Claim Rejections - 35 USC § 101

The prior rejection under 35 USC §101 of claims 18-23 is rendered moot in view of Applicants' cancellation of the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Newly added claims 36-52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-19, 21-25, 32-57, 60 and 61 of copending Application No. 09/260,468. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the instant application is directed to a method of cross-species nuclear transfer using differentiated human or mammalian cell or cell nucleus and an enucleated animal oocyte, and the '468 Application is directed to using an adult differentiated human cell or cell nucleus in an enucleated bovine oocyte. As such, the species of human differentiated cell and bovine oocyte makes obvious the genus of mammalian differentiated cell and animal oocyte.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The newly added claims are directed to methods of producing embryo-derived proliferating cells having human nuclear DNA and bovine-derived mitochondria, comprising the steps of (i) enucleating a bovine oocyte; (ii) inserting a human cell or cell nucleus into the bovine oocyte under conditions suitable for the formation of a NT unit; (iii) activating the resultant NT unit, (iv) culturing the activated NT unit to obtain a NT unit having at least 16 cells; and (v) culturing cells comprising the inner portion of the NT unit of step (iv) *in vitro* to obtain cells proliferating as a colony. In further embodiments, the claims are directed to isolated proliferated cells having human DNA and bovine-derived mitochondria.

The specification discloses the preparation of nuclear transfer units via a method of nuclear transfer of adult human epithelial cell nuclei into enucleated cattle oocytes to form a nuclear transfer (NT) unit (Figure 1) by electrofusion techniques. The methods disclosed in Example 1 of the specification result in the production of 1 NT unit (16-400 cell stage) according to Table 1, page 42.

Applicants' argue that the scope of the claim now accords with the unexpected discovery, described in Example 1, that the cells of the invention could even be produced. Applicants point to the specification to show that the cells would be used for studying cell differentiation and drug studies and that persons of skill in the art would recognize that the unusual cells produced by the invention, by virtue of having human nuclear DNA and bovine-derived mitochondrial (mtDNA) are useful in studying drugs that target cellular molecules that mediate mt-dependent

energy metabolism, and for identifying species-specific aspects of mitochondria-dependent energy metabolism. Applicants argue that persons of skilled in the art would also recognize that the cells produced by the instant invention would be useful for assaying the sensitivity of a human host immune system to transplanted syngenic and allogenic cells containing non-human mitochondria. Applicants argue that to the extent in which a human transplant recipient would accept the transplanted syngenic cells having non-human mitochondria is of great scientific and medical interest. Applicants argue that given the disclosure of a working example of the claimed invention in the application, one of skill in the art would reasonable expect to be able to follow the teachings of the specification and successfully use the claimed method to produce the claimed cells without undue experimentation. See p. 5 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. It is noted that the post-filing art supports that NT methodology may result in an embryo which contains both paternal and maternal mtDNA. Heteroplasmy can occur between sub-species, as supported by Meirelles *et al.* [**Genetics**, 158:351-356, May 2001] and Shitara *et al.* [**Genetics**, 156:1277-1284, November 2000]. Furthermore, the cited art of Meirelles *et al.* and Shitara *et al.,* clearly suggests that xenomitochondrial cybrids can be generated, however, due to incompatibilities and the inability of the cybrid to develop, the cross-species reconstituted embryos fail to develop past blastocyst stage [see Meirelles *et al.*, pp.

351-352, bridging paragraph]. Accordingly, in regard to xenomitochondrdial cybrids, as claimed by the present invention, the state of the art strongly suggests that even if the claimed invention resulted in a multicellular structure from which an embryo-derived, proliferating cell could be isolated and cultured, the mitochondria present in the viable embryonic cells would be from the same species as the donor, *i.e.,* compatible.

The specification teaches the production of only 1 NT unit, and fails to provide teachings or working examples with regard to the production of embryo-derived proliferating cells as required by the claims. The specification fails to show that the production of an NT unit having human nuclear DNA and bovine-derived mitochondrial DNA [and embryo-derived proliferating cells cultured from the NT unit] would be reproducible. One of skill in the art would be unable to rely upon the state of the art of cross-species NT because it is clearly unpredictable and as such, it is maintained that it would have required undue experimentation for one skilled in the art to make the claimed invention.

The claims, as amended, require "embryo-derived proliferating cells". The specification fails to provide support for what embryo-derived proliferating cells are, and what their phenotype is. If the claimed cells fail to be defined by a phenotype, or even what type(s) of cells they are, one would not know how to use them. Furthermore, the specification fails to provide teachings or guidance as to how to isolate the embryo-derived proliferating cells as claimed. For example, the claims

require that culturing cells comprising "the inner portion" of the NT unit produce embryo-derived proliferating cells. See claim 36, part (v). However, the specification fails to provide support as to what the "inner portion" of the NT unit is, and which cells would comprise the inner portion. As such, the specification fails to enable methods for making the claimed embryo-derived proliferating cells. Further, the specification fails to provide guidance or teachings for an enabled use for such cells. Although Applicants allege that the resulting cells can be used in methods such as studying drugs that target cellular molecules that mediate mitochondria-dependent energy metabolism, for example [see p. 5 of the Response], the specification fails to provide support for such uses.

It is reiterated that, in view of the supported undeveloped and unpredictable state of the art with respect to the characterization of cells produced by cross-species NT, Applicants' demonstration of the production of only one NT unit (Table 1) cannot be extrapolated to the production of embryo-derived cells as known in the art:

> *The courts have stated that:*
> *A specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir.1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However,* ***when there is no disclosure*** *of any specific starting material or* ***of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot***

> *be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constituteadequate enablement.* Genentech Inc. v. Novo Nordisk A/S, *42 USPQ2d 1005 (CAFC 1997) (emphasis added).*

In the instant case, Applicants fail to provide guidance to the skilled artisan on any parameters which would be necessary and critical for the production of embryo-derived cells having human DNA and bovine-derived mitochondria stem-like cells by the cross-species NT process.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation to producing embryo-derived proliferating cells having human DNA and bovine-derived mitochondria, the unpredictable and undeveloped state of the art with respect to cross-species nuclear transfer, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36 and 51, as written, are vague and indefinite. The claims recite the culturing of cells comprising the "inner portion" of the NT unit. See step (v) of the claim. This is vague because neither the claim nor the specification provide a definition for the term "inner portion". For example, which cells make up the inner portion of the NT unit? How many cells are in the inner portion? How much of the NT unit contains the inner portion? Claims 37-50 depend from claim 36. Claim 52 depends from claim 51.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48, 49, 50 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Heyneker *et al.* [WO 91/08216, published 13 June 1991].

The claims are directed to isolated proliferating cells having human nuclear DNA and bovine-derived mitochondria. Note that the claims are product-by-process claims. Where, as here, the claimed and prior art products are identical or

substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Heyneker *et al.* teach the generation of transgenic bovine species comprising a transgene encoding a recombinant DNA sequence, wherein the recombinant DNA sequence can encode human polypeptides such as industrial enzymes such as proteases, lipases, chitnases, etc. [see p. 12, 1st paragraph]. Heyneker *et al.* teach methods of generating the transgenic bovine species [see p. 28-29] and teach that before the transgenic embryos are implanted into recipient females, one cell is removed from each of the embryos and treated to release the DNA contained

therein. Each of these released DNAs are then digested to verify the presence of the transgene [see p. 8, lines 11-24]. As such, Heyneker *et al.* teach the limitations of the claims, because a transgenic cell that is isolated from an embryo would have genomic DNA which would include the human transgene, and mitochondria bovine DNA. As such, Heyneker *et al.* teach cells which are genetically altered with genomic human DNA than the mitochondrial DNA [bovine].

As such, Heyneker *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

TNT
Thái-An N. Ton
Patent Examiner
Group 1632